

# Care of Critically Ill Patients with COVID-19

(Last updated June 11, 2020)

## Summary Recommendations

### Infection Control:

- For health care workers who are performing aerosol-generating procedures on patients with COVID-19, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using fit-tested respirators (N95 respirators) or powered air-purifying respirators, rather than surgical masks, in addition to other personal protective equipment (i.e., gloves, gown, and eye protection such as a face shield or safety goggles) **(AIII)**.
- The Panel recommends that endotracheal intubation for patients with COVID-19 be performed by health care providers with extensive airway management experience, if possible **(AIII)**.
- The Panel recommends that intubation be achieved by video laryngoscopy, if possible **(CIII)**.

### Hemodynamic Support:

- The Panel recommends norepinephrine as the first-choice vasopressor **(AII)**.

### Ventilatory Support:

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV) **(BI)**.
- In the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure for whom HFNC is not available **(BIII)**.
- For adults with COVID-19 who are receiving supplemental oxygen, the Panel recommends close monitoring for worsening respiratory status and that intubation, if it becomes necessary, be performed by an experienced practitioner in a controlled setting **(AII)**.
- For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated, the Panel recommends considering a trial of awake prone positioning to improve oxygenation **(CIII)**.
- The Panel **recommends against** using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise require intubation and mechanical ventilation **(AIII)**.
- For mechanically ventilated adults with COVID-19 and acute respiratory distress syndrome (ARDS), the Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher tidal volumes (VT >8 mL/kg) **(AI)**.
- For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimized ventilation, the Panel recommends prone ventilation for 12 to 16 hours per day over no prone ventilation **(BII)**.
- For mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies, the Panel recommends using an inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off **(CIII)**.
- There are insufficient data to recommend either for or against the routine use of extracorporeal membrane oxygenation for patients with COVID-19 and refractory hypoxemia.

### Acute Kidney Injury and Renal Replacement Therapy:

- For critically ill patients with COVID-19 who have acute kidney injury and who develop indications for renal replacement therapy, the Panel recommends continuous renal replacement therapy (CRRT), if available **(BIII)**.
- If CRRT is not available or not possible due to limited resources, the Panel recommends prolonged intermittent renal replacement therapy rather than intermittent hemodialysis **(BIII)**.

### Drug Therapy:

- There are insufficient data for the Panel to recommend either for or against any immunomodulatory therapy in patients with severe COVID-19 disease.
- In patients with COVID-19 and severe or critical illness, there are insufficient data to recommend empiric broad-spectrum antimicrobial therapy in the absence of another indication.

- The Panel **recommends against** the routine use of systemic corticosteroids for the treatment of mechanically ventilated patients with COVID-19 without ARDS **(BIII)**.
- In mechanically ventilated adults with COVID-19 and ARDS, there are insufficient data to recommend either for or against corticosteroid therapy in the absence of another indication.
- For adults with COVID-19 and refractory shock, the Panel recommends using low-dose corticosteroid therapy (“shock-reversal”) over no corticosteroid **(BII)**.

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

# General Considerations

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## Co-Morbid Conditions

The vast majority of patients who are critically ill with COVID-19 have attributes and co-morbidities that place them at higher risk for serious disease, such as older age, hypertension, cardiovascular disease, diabetes, chronic respiratory disease, cancer, renal disease, and obesity.<sup>1</sup>

As with any patient in the intensive care unit (ICU), successful management depends on attention to the primary process leading to ICU admission, as well as to other co-morbidities and nosocomial complications.

## Bacterial Superinfection of COVID-19-Associated Pneumonia

Limited information exists about the frequency and microbiology of pulmonary coinfections and superinfections in patients with COVID-19, such as hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). Some studies from China emphasize the lack of bacterial coinfections in patients with COVID-19, while other studies suggest that these patients experience frequent bacterial complications.<sup>2-7</sup> There is appropriate concern about performing pulmonary diagnostic procedures, such as bronchoscopy or other airway sampling that requires disruption of a closed airway circuit. Thus, while some clinicians do not routinely start empiric broad-spectrum antimicrobial therapy for COVID-19 patients with severe disease, other experienced clinicians routinely use such therapy. For the treatment of shock, however, broad-spectrum empiric antimicrobial therapy is standard of care. Antibiotic stewardship is critical to avoid reflexive or continued courses of antibiotics.

## Septic Shock and Cytokine Storm Due to COVID-19

Patients with COVID-19 may express high levels of an array of inflammatory cytokines, often in the setting of deteriorating hemodynamic or respiratory status. This is often referred to as “cytokine release syndrome” or “cytokine storm,” although these are imprecise terms. Intensivists need to consider the full differential diagnosis of shock to exclude other treatable causes of shock (e.g., bacterial sepsis due to pneumonia or an extra-pulmonary source, hypovolemic shock due to a gastrointestinal hemorrhage that is unrelated to COVID-19, cardiac dysfunction related to COVID-19 or comorbid atherosclerotic disease, stress-related adrenal insufficiency).

## COVID-19-Induced Cardiac Dysfunction, Including Myocarditis

There is a growing body of literature relating COVID-19 to myocarditis and pericardial dysfunction in approximately 20% of patients.<sup>3,5,8-11</sup> Acute cardiac injury and arrhythmias have also been described in patients with COVID-19.

## Renal and Hepatic Dysfunction Due to COVID-19

Although SARS-CoV-2 is primarily a pulmonary pathogen, renal and hepatic dysfunction are consistently described in patients with severe disease.<sup>3</sup> Continuous renal replacement therapy was needed in more than 15% of cases of critical disease in one series.<sup>5</sup>

## Drug-Drug Interactions Between Drugs Used to Treat COVID-19 and Drugs Used to Treat Co-Morbidities

All ICU patients should routinely be monitored for drug-drug interactions. The potential for drug-drug

interactions between investigational or off-label medications used to treat COVID-19 and concurrent drugs should be considered. QTc prolongation due to agents such as chloroquine or hydroxychloroquine is a potential problem for patients with underlying heart disease and/or those who concurrently use drugs that prolong the QTc interval (e.g., azithromycin, quinolones).

## Other Intensive Care Unit-Related Complications

Patients who are critically ill with COVID-19 are at risk for nosocomial infections and other complications of critical illness care, such as VAP, HAP, catheter-related bloodstream infections, and venous thromboembolism. The focus on COVID-19 should not reduce attention to minimizing conventional ICU complications in order to optimize the likelihood of a successful ICU outcome.

## Goals of Care

For any critically ill patient, the goals of care must be assessed when the patient is admitted and regularly thereafter. This is essential regardless of the availability of resources, the age of the patient, or the patient's co-morbid conditions.<sup>12,13</sup>

The Surviving Sepsis Campaign (SSC), an initiative supported by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, issued *Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)* in March 2020.<sup>14</sup> The COVID-19 Treatment Guidelines Panel (the Panel) has based these recommendations on the SSC COVID-19 Guidelines, with permission, and the Panel gratefully acknowledges the work of the SSC COVID-19 Guidelines Panel. The Panel also acknowledges the contributions and expertise of Andrew Rhodes, MBBS, MD, of St. George's University Hospitals in London, England, and Waleed Alhazzani, MBBS, MSc, of McMaster University in Hamilton, Canada.

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# Infection Control

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Health care workers should follow the infection control policies and procedures issued by their health care institutions.

## Recommendation:

- For health care workers who are performing aerosol-generating procedures on patients with COVID-19, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using fit-tested respirators (N95 respirators) or powered air-purifying respirators rather than surgical masks, in addition to other personal protective equipment (PPE) (i.e., gloves, gown, and eye protection, such as a face shield or safety goggles) **(AIII)**.
- Aerosol-generating procedures include endotracheal intubation and extubation; bronchoscopy; open suctioning; high-flow nasal cannula (HFNC) or face mask; nebulizer treatment; manual ventilation; physical proning of the patient; disconnecting a patient from a ventilator; mini-bronchoalveolar lavage; noninvasive positive pressure ventilation (NIPPV); tracheostomy; or cardiopulmonary resuscitation.

## Rationale

During the severe acute respiratory syndrome (SARS) epidemic, aerosol-generating procedures increased the risk of infection among health care workers.<sup>1,2</sup> N95 respirators block 95% to 99% of aerosol particles; however, staff must be fit-tested for the type used. Surgical masks block large particles, droplets, and sprays, but are less effective in blocking small particles (<5 µm) and aerosols.<sup>3</sup>

## Recommendation:

- The Panel recommends minimizing the use of aerosol-generating procedures on COVID-19 intensive care unit patients and carrying out any necessary aerosol-generating procedures in a negative-pressure room, also known as an airborne infection isolation room (AIIR) **(AIII)**.

## Rationale

AIIRs lower the risk of cross-contamination among rooms and lower the risk of infection for staff and patients outside the room when aerosol-generating procedures are performed. AIIRs were effective in preventing virus spread during the SARS epidemic.<sup>2</sup> If an AIIR is not available, a high-efficiency particulate air (HEPA) filter should be used, especially for patients on HFNC or noninvasive ventilation. HEPA filters reduce virus transmission in simulations.<sup>4</sup>

## Recommendations:

- For health care workers who are providing usual care for non-ventilated COVID-19 patients, the Panel recommends using surgical masks or fit-tested respirators (N95 respirators), in addition to other PPE (i.e., gloves, gown, and eye protection, such as a face shield or safety goggles) **(AII)**.
- For health care workers who are performing non-aerosol-generating procedures on patients with COVID-19 who are on closed-circuit mechanical ventilation, the Panel recommends using surgical masks or fit-tested respirators (N95 respirators), in addition to other PPE (i.e., gloves, gown, and eye protection, such as a face shield or safety goggles) **(AII)**.

## Rationale

There is evidence from viral diseases including SARS that both surgical masks and N95 masks reduce



transmission of infection.<sup>5</sup> Current evidence suggests that surgical masks are probably not inferior to N95 respirators for preventing transmission of laboratory-confirmed seasonal respiratory viral infections (e.g., influenza).<sup>6,7</sup> The Surviving Sepsis Campaign COVID-19 Guidelines updated a recent systematic review and meta-analysis of randomized controlled trials that demonstrated no statistical difference in protection between surgical masks and N95 respirators in this setting.<sup>8</sup>

## Recommendations:

- The Panel recommends that endotracheal intubation for patients with COVID-19 be performed by health care providers with extensive airway management experience, if possible (**AIII**).
- The Panel recommends that intubation be achieved by video laryngoscopy, if possible (**CIII**).

## Rationale

Factors that maximize the chances of first-pass success and minimize aerosolization should be used when intubating patients with suspected or confirmed COVID-19.<sup>9,10</sup> Thus, the Panel recommends that the health care operator with the most experience and skill in airway management be the first to attempt intubation. The close facial proximity of direct laryngoscopy can expose health care providers to higher concentrations of viral aerosols. Finally, it is important to avoid having unnecessary staff in the room.

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# Laboratory Diagnosis

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## Recommendations:

- For intubated and mechanically ventilated adults who are suspected to have COVID-19 but who do not have a confirmed diagnosis:
  - The COVID-19 Treatment Guidelines Panel (the Panel) recommends obtaining lower respiratory tract samples to establish a diagnosis of COVID-19 over upper respiratory tract (nasopharyngeal or oropharyngeal) samples **(BII)**.
  - The Panel recommends obtaining endotracheal aspirates over bronchial wash or bronchoalveolar lavage (BAL) samples when obtaining lower respiratory samples to establish a diagnosis of COVID-19 **(BII)**.

## Rationale

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses several diagnostic challenges, including potentially discordant shedding of virus from the upper versus lower respiratory tract. COVID-19 diagnosis is currently based on using a reverse transcriptase polymerase chain reaction (RT-PCR) assay to detect viral RNA in respiratory samples. The high specificity of RT-PCR removes the need for lower respiratory tract samples to diagnose COVID-19 when a nasopharyngeal swab is positive for a patient with recent onset of the disease. Lower respiratory tract specimens are considered by some experts to have higher yield, due to high viral load, consistent with what has been observed for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).<sup>1-7</sup> Thus, lower respiratory tract samples should be obtained whenever possible if there is diagnostic uncertainty regarding COVID-19.

However, BAL and sputum induction are aerosol-generating procedures and should be performed only with careful consideration of the risk to staff of aerosol generation. Endotracheal aspirates appear to carry a lower risk of aerosolization than BAL and are thought by some experts to have comparable sensitivity and specificity to BAL specimens.

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# Hemodynamics

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For the most part, these hemodynamic recommendations are similar to those previously published in the *Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016*. Ultimately, COVID-19 patients who require fluid resuscitation or hemodynamic management of shock should be treated and managed identically to those with septic shock.<sup>1</sup>

COVID-19 patients who require fluid resuscitation or hemodynamic management of shock should be treated and managed for septic shock in accordance with other published guidelines, with the following exceptions.

## Recommendation:

- For adults with COVID-19 and shock, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using dynamic parameters, skin temperature, capillary refilling time, and/or lactate over static parameters to assess fluid responsiveness (**BII**).

## Rationale

No direct evidence addresses the optimal resuscitation strategy for patients with COVID-19 and shock. In a systematic review and meta-analysis of 13 non-COVID-19 randomized clinical trials ( $n = 1,652$ ),<sup>2</sup> dynamic assessment to guide fluid therapy reduced mortality (risk ratio 0.59; 95% confidence interval [CI], 0.42–0.83), intensive care unit (ICU) length of stay (mean duration -1.16 days; 95% CI, -1.97 to -0.36), and duration of mechanical ventilation (weighted mean difference -2.98 hours; 95% CI, -5.08 to -0.89). Dynamic parameters used in these trials included stroke volume variation (SVV), pulse pressure variation (PPV), and stroke volume change with passive leg raise or fluid challenge. Passive leg raising, followed by PPV and SVV, appears to predict fluid responsiveness with the highest accuracy.<sup>3</sup> The static parameters included components of early goal-directed therapy (e.g., central venous pressure, mean arterial pressure).

Resuscitation of non-COVID-19 patients with shock based on serum lactate levels has been summarized in a systematic review and meta-analysis of seven randomized clinical trials ( $n = 1,301$ ). Compared with central venous oxygen saturation ( $ScVO_2$ )-guided therapy, early lactate clearance-directed therapy was associated with a reduction in mortality (relative ratio 0.68; 95% CI, 0.56–0.82), shorter length of ICU stay (mean difference -1.64 days; 95% CI, -3.23 to -0.05), and shorter duration of mechanical ventilation (mean difference -10.22 hours; 95% CI, -15.94 to -4.50).<sup>4</sup>

## Recommendation:

- For the acute resuscitation of adults with COVID-19 and shock, the Panel recommends using buffered/balanced crystalloids over unbalanced crystalloids (**BII**).

## Rationale

A pragmatic randomized trial that compared balanced and unbalanced crystalloids in 15,802 critically ill adults found a lower rate of a composite outcome, including death, new renal-replacement therapy, or persistent renal dysfunction (odds ratio [OR] 0.90; 95% CI, 0.82–0.99;  $P = 0.04$ ).<sup>5</sup> The subset of sepsis patients in this trial ( $n = 1,641$ ) was found to have a lower mortality (adjusted odds ratio 0.74; 95% CI, 0.59–0.93;  $P = 0.01$ ), as well as fewer days requiring vasopressors and renal replacement therapy.<sup>6</sup> A subsequent meta-analysis of 21 randomized controlled trials ( $n = 20,213$ ) that compared balanced crystalloids to 0.9% saline for resuscitation of critically ill adults and children reported nonsignificant

differences in hospital mortality (OR 0.91; 95% CI, 0.83–1.01) and acute kidney injury (OR 0.92; 95% CI, 0.84–1.00).<sup>7</sup>

## Recommendation:

- For the acute resuscitation of adults with COVID-19 and shock, the Panel **recommends against** the initial use of albumin for resuscitation (**BI**).

## Rationale

A meta-analysis of 20 non-COVID-19 randomized controlled trials (n = 13,047) that compared the use of albumin or fresh-frozen plasma to crystalloids in critically ill patients found no difference in all-cause mortality,<sup>8</sup> while a meta-analysis of 17 non-COVID-19 randomized controlled trials (n = 1,977) that compared the use of albumin to crystalloids specifically in patients with sepsis observed a reduction in mortality (OR 0.82; 95% CI, 0.67–1.0; *P* = 0.047).<sup>9</sup> Given the higher cost of albumin and the lack of a definitive clinical benefit, the Panel suggests avoiding the use of albumin for initial, routine resuscitation of patients with COVID-19 and shock.

## Additional Recommendations Based on General Principles of Critical Care:

- The Panel **recommends against** using hydroxyethyl starches for intravascular volume replacement in patients with sepsis or septic shock (**AI**).
- The Panel recommends norepinephrine as the first-choice vasopressor (**AII**). The Panel recommends adding either vasopressin (up to 0.03 U/min) (**BII**) or epinephrine (**CII**) to norepinephrine to raise mean arterial pressure to target, or adding vasopressin (up to 0.03 U/min) (**CII**) to decrease norepinephrine dosage.
- When norepinephrine is available, the Panel **recommends against** using dopamine for patients with COVID-19 and shock (**AI**).
- The Panel **recommends against** using low-dose dopamine for renal protection (**BII**).
- The Panel recommends using dobutamine in patients who show evidence of cardiac dysfunction and persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (**BII**).
- The Panel recommends that all patients who require vasopressors have an arterial catheter placed as soon as practical, if resources are available (**BIII**).
- For adults with COVID-19 and refractory shock, the Panel recommends using low-dose corticosteroid therapy (“shock-reversal”) over no corticosteroid (**BII**).
  - A typical corticosteroid regimen in septic shock is intravenous hydrocortisone 200 mg per day administered either as an infusion or intermittent doses. The duration of hydrocortisone therapy is usually a clinical decision.

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# Oxygenation and Ventilation

(Last updated June 11, 2020)

For hypoxemic patients, the recommendations below emphasize well-described and documented recommendations from the Surviving Sepsis Campaign Guidelines for [adult sepsis](#), [pediatric sepsis](#), and [COVID-19](#), which provide more details about management and the data that support the recommendations.

## Recommendations

- For adults with COVID-19 who are receiving supplemental oxygen, the COVID-19 Treatment Guidelines Panel (the Panel) recommends close monitoring for worsening respiratory status and that intubation, if it becomes necessary, be performed by an experienced practitioner in a controlled setting (**AII**).
- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV) (**BI**).
- In the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure for whom HFNC is not available (**BIII**).
- For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated, the Panel recommends considering a trial of awake prone positioning to improve oxygenation (**CIII**).
- The Panel **recommends against** using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise require intubation and mechanical ventilation (**AIII**).

## Rationale

Hypoxemia is common in hospitalized patients with COVID-19. The criteria for hospital admission, intensive care unit (ICU) admission, and mechanical ventilation differ between countries. In some hospitals in the United States, >25% of hospitalized patients require ICU care, mostly due to acute respiratory failure.<sup>1-5</sup>

In adults with COVID-19 and acute hypoxemic respiratory failure, conventional oxygen therapy may be insufficient to meet the oxygen needs of the patient. Options include HFNC, NIPPV, or intubation and invasive mechanical ventilation.

HFNC and NIPPV are preferable to conventional oxygen therapy based on data from non-COVID-19 clinical trials and meta-analyses that showed reductions in the need for therapeutic escalation and the need for intubation in patients who received HFNC or NIPPV.<sup>6,7</sup>

HFNC is preferred over NIPPV in patients with acute hypoxemic respiratory failure based on data from an unblinded clinical trial that was performed prior to the COVID-19 pandemic. This trial found more ventilator-free days with HFNC than with conventional oxygen therapy or NIPPV (24 days vs. 22 days vs. 19 days, respectively;  $P = 0.02$ ) and lower 90-day mortality with HFNC than with both conventional oxygen therapy (hazard ratio [HR] 2.01; 95% confidence interval [CI], 1.01–3.99) and NIPPV (HR 2.50; 95% CI, 1.31–4.78).<sup>8</sup>

In the subgroup of more severely hypoxemic patients with  $\text{PaO}_2/\text{FiO}_2 \leq 200$ , HFNC reduced the rate

of intubation compared to conventional oxygen therapy or NIPPV (HRs 2.07 and 2.57, respectively). These findings were corroborated in a meta-analysis that showed a lower likelihood of intubation (odds ratio [OR] 0.48; 95% CI, 0.31–0.73) and ICU mortality (OR 0.36; 95% CI, 0.20–0.63) with HFNC than with NIPPV.<sup>9</sup> In situations where the options for respiratory support are limited, reducing the need for intubation may be particularly important.

Prone positioning improves oxygenation and patient outcomes in patients with moderate-to-severe acute respiratory distress syndrome (ARDS) that requires mechanical ventilation.<sup>10,11</sup> Prone positioning is thought to improve oxygenation because it improves ventilation-perfusion matching and recruits collapsed alveoli in the dorsal lungs.<sup>12</sup> Two case series that were published prior to the COVID-19 pandemic reported improved oxygenation and low intubation rates when placing spontaneously breathing patients with hypoxemia in the prone position,<sup>13,14</sup> and several new case series reported similar results with awake prone positioning in patients with COVID-19 pneumonia who required supplemental oxygen.

In a case series of 50 patients with COVID-19 pneumonia who required supplemental oxygen upon presentation to a New York City emergency department (ED), awake prone positioning improved overall median oxygen saturation. However, 13 of these patients still required intubation due to respiratory failure within 24 hours of presentation to the ED.<sup>15</sup> Another case series from Jiangsu province used awake prone positioning as part of a treatment strategy in nonintubated patients with COVID-19 pneumonia and reported an intubation rate of less than 1%.<sup>16</sup> In a report of 24 patients who required either a nasal cannula or HFNC and who had a chest computerized tomography scan that was consistent with COVID-19 pneumonia, 25% of patients tolerated prone positioning for at least 3 hours and showed >20% improvement in the partial pressure of oxygen in arterial blood. No complications were reported with prone positioning.<sup>17</sup> Another case series of 15 patients with ARDS due to COVID-19 pneumonia who received awake prone positioning while on noninvasive ventilation reported that all patients showed improvement in their oxygen saturation during prone positioning, with 80% of patients sustaining improved oxygenation with resupination. Seven percent of patients required intubation.<sup>18</sup>

Appropriate candidates for awake prone positioning are those who are able to adjust their position independently and tolerate lying prone. Awake prone positioning is contraindicated in patients who are in respiratory distress and who require immediate intubation. Awake prone positioning is also contraindicated in hemodynamically unstable patients, patients who recently had abdominal surgery, and patients who have an unstable spine.<sup>19</sup> Awake prone positioning is acceptable and feasible for pregnant patients and can be performed in the left lateral decubitus position or the fully prone position.<sup>20</sup>

It is essential that hypoxemic patients with COVID-19 be monitored closely for signs of respiratory decompensation. To ensure the safety of both the patient and health care workers, intubation should be performed in a controlled setting by an experienced practitioner.

Early intubation may be particularly appropriate when patients have additional acute organ dysfunction or chronic comorbidities, or when HFNC and NIPPV are not available. NIPPV has a high failure rate in both patients with non-COVID-19 viral pneumonia<sup>21,22</sup> and patients with ARDS.<sup>23,24</sup> NIPPV may generate aerosol spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and thus increase nosocomial transmission of the infection.<sup>25,26</sup> It remains unclear whether HFNC results in a lower risk of nosocomial SARS-CoV-2 transmission.

The use of supplemental oxygen in adults with COVID-19 has not been studied, but indirect evidence from other critical illnesses suggests the optimal oxygen target is an SpO<sub>2</sub> between 92% and 96%:

- A meta-analysis of 25 randomized controlled trials found that a liberal oxygen strategy (median SpO<sub>2</sub> 96%) was associated with an increased risk of hospital mortality (relative risk 1.21; 95% CI, 1.03–1.43).<sup>27</sup>



- The LOCO2 randomized controlled trial compared a conservative oxygen strategy (target SpO<sub>2</sub> 88% to 92%) to a liberal oxygen strategy (target SpO<sub>2</sub> ≥96%).<sup>28</sup> The trial was stopped early due to futility. Mortality was increased among those who received the conservative oxygen therapy at Day 28 (risk difference +8%; 95% CI, -5% to +21%) and Day 90 (risk difference +14%; 95% CI, +0.7% to +27%). These differences would be important if they were real, but the study was too small to definitively confirm or exclude an effect.

## Recommendations

For mechanically ventilated adults with COVID-19 and ARDS:

- The Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher tidal volumes (VT >8 mL/kg) (**AI**).
- The Panel recommends targeting plateau pressures of <30 cm H<sub>2</sub>O (**AII**).
- The Panel recommends using a conservative fluid strategy over a liberal fluid strategy (**BII**).
- The Panel **recommends against** the routine use of inhaled nitric oxide (**AI**).

## Rationale

Currently, there is no evidence that ventilator management of patients with ARDS due to COVID-19 should differ from the management of patients with viral pneumonia due to influenza or other respiratory viruses.

## Recommendations

For mechanically ventilated adults with COVID-19 and moderate-to-severe ARDS:

- The Panel recommends using a higher positive end-expiratory pressure (PEEP) strategy over a lower PEEP strategy (**BII**).
- For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimized ventilation, the Panel recommends prone ventilation for 12 to 16 hours per day over no prone ventilation (**BII**).

## Rationale

Prone positioning is a recommended strategy in non-COVID-19-related ARDS for improving oxygenation and reducing the heterogeneity of lung ventilation. Prone positioning has been used to treat patients with COVID-19, although there is currently not enough clinical experience with this strategy to draw conclusions about its effect on long-term outcomes.<sup>29</sup> However, even in centers that are experienced in prone ventilation, prone positioning requires multiple staff members to safely turn the patient and prevent dislodgement of the endotracheal tube, as well as other tubes and catheters. Each staff member should wear the recommended personal protective equipment (PPE). Depending on local resources, especially when PPE may be in short supply, the risk of COVID-19 exposure during the process of prone positioning may outweigh the benefit of prone positioning to the patient. Prone positioning is acceptable and feasible for pregnant patients who are mechanically ventilated, and it can be performed in the left lateral decubitus position or the fully prone position.<sup>20</sup>

## Recommendations

- The Panel recommends using, as needed, intermittent boluses of neuromuscular blocking agents (NMBA) or continuous NMBA infusion to facilitate protective lung ventilation (**BIII**).
- In the event of persistent patient-ventilator dyssynchrony, which places the patient at risk for

ventilator lung injury, or in cases where a patient requires ongoing deep sedation, prone ventilation, or persistently high plateau pressures, the Panel recommends using a continuous NMBA infusion for up to 48 hours as long as patient anxiety and pain can be adequately monitored and controlled (**BIII**).

## Rationale

The recommendation for intermittent boluses of NMBA or continuous infusion of NMBA to facilitate lung protection may require a health care provider to enter the patient's room more frequently for close clinical monitoring. Therefore, in some situations, the risks of COVID-19 exposure and the use of PPE for each entry may outweigh the benefit of NMBA treatment.

## Recommendations

For mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies:

- The Panel recommends using recruitment maneuvers rather than not using recruitment maneuvers (**CII**).
- If recruitment maneuvers are used, the Panel **recommends against** using staircase (incremental PEEP) recruitment maneuvers (**AII**).
- The Panel recommends using an inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off (**CIII**).

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# Acute Kidney Injury and Renal Replacement Therapy

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(Last updated June 11, 2020)

## Recommendations

- For critically ill patients with COVID-19 who have acute kidney injury (AKI) and who develop indications for renal replacement therapy (RRT), the COVID-19 Treatment Guidelines Panel (the Panel) recommends continuous renal replacement therapy (CRRT), if available **(BIII)**.
- If CRRT is not available or not possible due to limited resources, the Panel recommends prolonged intermittent renal replacement therapy (PIRRT) rather than intermittent hemodialysis (IHD) **(BIII)**.

## Rationale

AKI that requires RRT occurs in approximately 22% of patients with COVID-19 who are admitted to the intensive care unit.<sup>1</sup> Evidence pertaining to RRT in patients with COVID-19 is scarce. Until additional evidence is available, the Panel suggests using the same indications for RRT in patients with COVID-19 as those used for other critically ill patients.<sup>2</sup>

RRT modalities have not been compared in COVID-19 patients; the Panel's recommendations are motivated by the desire to minimize the risk of viral transmission to health care workers. The Panel considers CRRT to be the preferred RRT modality. CRRT is preferable to PIRRT because medication dosing for CRRT is more easily optimized and CRRT does not require nursing staff to enter the patient's room to begin and end dialysis sessions. CRRT and PIRRT are both preferable to IHD because neither requires a dedicated hemodialysis nurse. Peritoneal dialysis has also been used during surge situations in patients with COVID-19.

In situations where there may be insufficient CRRT machines or equipment to meet demand, the Panel advocates performing PIRRT instead of CRRT, and then using the machine for another patient after appropriate cleaning.

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# Pharmacologic Interventions

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(Last updated April 21, 2020)

## Recommendations:

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against any immunomodulatory therapy in COVID-19 patients with severe disease (**AIII**).
- There are insufficient data for the Panel to recommend either for or against the use of interleukin 6 (IL-6) antagonists (e.g., sarilumab, siltuximab, tocilizumab) for the treatment of COVID-19 (**AIII**).

## Rationale

IL-6 is a pleiotropic, pro-inflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by the related SARS-CoV induces a dose-dependent production of IL-6 from bronchial epithelial cells.<sup>1</sup>

Elevations in IL-6 levels may be an important mediator when severe systemic inflammatory responses occur in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. COVID-19-associated systemic inflammation and hypoxic respiratory failure is associated with heightened cytokine release as indicated by elevated blood levels of IL-6 and C-reactive protein, but typically not procalcitonin.

There are no data from randomized clinical trials or large observational cohort studies describing the efficacy of tocilizumab among patients with COVID-19. There are anecdotal reports of improved oxygenation in patients with COVID-19, systemic inflammation, and hypoxic respiratory failure.

The primary laboratory abnormalities reported with tocilizumab treatment are elevated levels of liver enzymes that appear to be dose dependent. Neutropenia or thrombocytopenia are uncommon. Additional adverse events, such as risk for serious infections (e.g., tuberculosis, other bacterial pathogens), have been reported only in the context of continuous dosing of tocilizumab.<sup>2-7</sup>

Clinicians have used tocilizumab for desperately ill patients. The results of ongoing trials will enable clinicians to make evidence-based decisions about whether to use this drug and how to best use it.

## Recommendations:

- The Panel **recommends against** the routine use of systemic corticosteroids for the treatment of mechanically ventilated patients with COVID-19 without acute respiratory distress syndrome (ARDS) (**BIII**).
- In mechanically ventilated adults with COVID-19 and ARDS, there are insufficient data to recommend either for or against corticosteroid therapy in the absence of another indication (**CI**).

## Rationale

No randomized clinical trials of corticosteroid use in patients with COVID-19, including those with severe disease, have been performed.

Cytokine elevations have been described in patients with severe COVID-19 pneumonia; thus, clinicians have used corticosteroids to treat severe COVID-19.<sup>8,9</sup> In addition, the anti-inflammatory properties of corticosteroids may help suppress the inflammatory and cytokine-related lung injury that is characteristic



of ARDS.

Prior experience with influenza and other coronaviruses may be relevant. A recent Cochrane analysis of influenza pneumonia demonstrated increased mortality and increased incidence of hospital-acquired pneumonia (HAP) in patients who were administered corticosteroids.<sup>10</sup> The analysis was confounded by study heterogeneity, including different dosage regimens and different durations of therapy for corticosteroid interventions.

For Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), and influenza, some studies have demonstrated an association between corticosteroid use and delayed viral clearance.<sup>11-13</sup>

Limited data have been published from uncontrolled studies that used varying doses and durations of corticosteroid therapy for COVID-19. A recent retrospective series of patients with COVID-19 and associated ARDS observed, in an unadjusted analysis, a decrease in mortality (hazard ratio 0.38; 95% confidence interval, 0.20–0.72) with methylprednisolone, but there were confounding factors in this analysis.<sup>14</sup>

In the absence of ARDS, the routine use of corticosteroids is not recommended, although patients with COVID-19 may have other indications to receive corticosteroids, including refractory shock or myocarditis.<sup>10,15</sup>

Clinicians have used corticosteroids in severe and critical COVID-19.<sup>14</sup> The results of ongoing trials will enable clinicians to make evidence-based decisions about whether to use this drug and will help define the optimal timing, dose, and duration of corticosteroid therapy in patients with COVID-19, including those with ARDS (a list of these clinical trials is available on [ClinicalTrials.gov](https://clinicaltrials.gov)).

## Recommendations:

- In patients with COVID-19 and severe or critical illness, there are insufficient data to recommend empiric broad-spectrum antimicrobial therapy in the absence of another indication (**BIII**).
- If antimicrobials are initiated, the Panel recommends that their use should be reassessed daily in order to minimize the adverse consequences of unnecessary antimicrobial therapy (**AIII**).

## Rationale

There are no reliable estimates of the incidence or prevalence of co-pathogens with COVID-19 at this time.

For patients with COVID-19, some experts routinely administer broad-spectrum antibiotics to all patients with moderate or severe hypoxemia. Other experts administer antibiotics only for specific situations, such as the presence of a lobar infiltrate on chest x-ray, leukocytosis, an elevated serum lactate, microbiologic data, or shock.

Gram stain and cultures or testing of respiratory specimens are often not available due to concern about aerosolization of virus during diagnostic procedures or when processing specimens.

There are no clinical trials that have evaluated the use of empiric antimicrobial agents in patients with COVID-19 or other severe coronavirus infections.

With influenza, empiric antibacterial treatment is strongly recommended for patients with initial severe disease (i.e., those with extensive pneumonia, respiratory failure, hypotension, and fever) and those who deteriorate after initial improvement.<sup>16</sup> These recommendations are based on observations that bacterial

superinfections, especially those due to *Staphylococcus aureus* and *Streptococcus pneumoniae*, are not uncommon and have dire consequences if not treated promptly.

Whether moderate or severe COVID-19 disease should be approached like severe influenza will remain uncertain until more microbiologic and clinical data become available.

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# Extracorporeal Membrane Oxygenation

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(Last updated April 21, 2020)

## Recommendation:

- There are insufficient data to recommend either for or against the routine use of extracorporeal membrane oxygenation (ECMO) for patients with COVID-19 and refractory hypoxemia (**BIII**).

## Rationale

While ECMO may serve as an effective short-term rescue therapy in patients with severe acute respiratory distress syndrome and refractory hypoxemia, there is no conclusive evidence that ECMO is responsible for better clinical outcomes in patients who received ECMO than in patients who did not receive ECMO.<sup>1-4</sup>

ECMO is used by some experts, when available, for patients with refractory hypoxemia despite optimization of ventilation strategies and adjunctive therapies. Ideally, clinicians who are interested in using ECMO should either try to enter their patient into clinical trials or clinical registries so that more informative data can be obtained. The following resources provide more information on the use of ECMO in patients with COVID-19:

- [Extracorporeal Life Support Organization](#)
- [Clinical trials evaluating ECMO in patients with COVID-19](#) on [ClinicalTrials.gov](#).

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